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International Journal of Global Health and Health Disparities

Volume 3 | Number 1 Article 7

2004

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Jorge E. Galva
University of Iowa

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Recommended Citation

Galva, Jorge E. (2004) "Severe Acute Respiratory Syndrome : Description, Epidemiology, and Control Measures," *International Journal of Global Health and Health Disparities, 3(1),* 63-72.
Available at: https://scholarworks.uni.edu/ijghhd/vol3/iss1/7

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Galva: Severe Acute Respiratory Syndrome : Description, Epidemiology, an

SEVERE ACUTE RESPIRATORY SYNDROME: DESCRIPTION, EPIDEMIOLOGY AND CONTROL MEASURES

Jorge E. Galva, J.D., M.H.A.
The University of Iowa Hospitals and Clinics
Iowa City, Iowa, U.S.A.

Severe Acute Respiratory Syndrome (hereinafter SARS) is the first severe and readily transmissible new disease to emerge in the 21st century1. The presence of this infectious agent was first recognized in early November 2002 in the province of Guangdong in the People's Republic of China. SARS rapidly spread from there to other parts of the world, notably Southeast Asia and Canada. According to data compiled in August 2003, altogether 8,422 cases occurred in 29 countries. The most severely affected countries were China (including the Special Administrative Region of Hong Kong and Taiwan), Canada, Singapore and Vietnam, all of which experienced outbreaks before the issue of global alerts by the World Health Organization (WHO) on 12 and 15 March, 2003. Nine hundred and eight persons died in the most affected countries, with only eight deaths occurring in the additional 25 countries where cases were reported.

International public health authorities took immediate steps to isolate and identify the pathogen responsible for the atypical severe pneumonia. The coronavirus (SARS-CoV) was ultimately identified as the pathogen responsible . Vigorous, even drastic, national and international public health measures contributed to the rapid control of the infection. On July 5, 2003, WHO announced that the last known chain of human-to-human transmission of the SARS virus had been broken; this brought to an end the initial outbreak of this new and severe respiratory disease2. International public health organizations remain alert to the possibility of re-emergence of the virus despite the subsidence and eventual disappearance of new infection reports.

There exist ample unknown elements to the SARS outbreak. Epidemiologists have yet to definitely ascertain the origin of the pathogen, the precise mechanism of infection and the possible seasonality or environmental conditioners to re-emergence. Public health authorities were able to contain the outbreak through extremely successful albeit low-tech methods; these were greatly effective but exacted tremendous economic and personal hardship and disruption to millions of persons. The possibility of preventive measures such as vaccines is still remote.

The SARS outbreak is a prime example of the sudden emergence of a suspected trans-species pathogen able to survive within the human host with extremely prejudicial effects on human health. Careful analysis of the appearance, detection, alert and remedial methods used to control the SARS epidemic remain of the utmost importance.

BACKGROUND OF THE DISEASE

The first known case of atypical pneumonia occurred in Foshan City, Guangdong Province, People's Republic of China on November 16, 2002. WHO received reports of the Chinese Ministry of Health of an outbreak in that province with 305 known cases and five fatalities on February 11, 2003. The Chinese government informed WHO on February 12, 2003, that the outbreak had now affected six municipalities; tests for influenza viruses had come negative. Further investigations over the course of

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monary plague, leptospirosis and hemorrhagic fever. The Chinese public health authorities, for the first time, designated the disease as atypical pneumonia of unknown origin

On February 20, Hong Kong officials informed WHO of an outbreak of two cases of avian influenza following the detection of A(H5N1) virus in members of a family recently returned from Guangdong. On February 26, a foreign businessman was admitted to the French Hospital in Hanoi, Republic of Vietnam, with a three-day history of respiratory symptoms; the patient had been on a business trip to Hong Kong. Two days later Dr. Carlo Urbani, a WHO official based in Vietnam, was alarmed by several cases of atypical pneumonia in the French Hospital, where he assisted as consultant; Dr. Urbani notified the WHO Regional Office for the Western Pacific.

On March 1, 2003, a former flight attendant was admitted to a hospital in Singapore with diagnosis of respiratory syndrome of unknown origin. The flight attendant had been on a trip to Hong Kong. Four days later, the businessman hospitalized in Hanoi was transferred to the Princess Margaret Hospital in Hong Kong; by then, seven health workers at the French Hospital had become ill with atypical pneumonia. On that same day a Toronto woman returning to Canada after a trip to Hong Kong died; five members of her family were found to be infected and were admitted for hospital care. On March 11, Dr. Urbani departed for Bangkok for a presentation on tropical diseases; he was ill on arrival and was immediately hospitalized5. In the aftermath of the epidemic, public health authorities determined that the virus spread from its original point of presumed inception in Guangdong province to the following countries or regions (in order of detection and/or reporting): Guangdong province, Hong Kong, Vietnam, Singapore, Germany, Canada, Hong Kong (secondary), the United States and Ireland2:

On March 12, 2003, WHO issued a global alert about cases of severe atypical pneumonia following mounting and increasingly alarming reports of cases among hospital staff members in Hanoi and Hong Kong. The next day WHO activated its emergency alert system, sending urgent messages to all Global Outbreak Alert and Response Network (GOARN) partners. GOARN was launched in 2000 as a mechanism to link together 112 existing networks which possessed much of the data, expertise and skills to keep the international community abreast of outbreaks and ready to respond. GOARN would turn out to be one of the most important instruments in combating the rapidly spreading disease. The GOARN alert represented the first global recognition of the severe nature of this deadly threat. WHO was on the track of a new and highly contagious form of pneumonia. The race to stop the disease had started.

CASE DEFINITION:

The public health response to SARS depended on the rapid development of means to promptly identify suspect cases and differentiate these from known entities with similar symptoms. In order to do this, information was rapidly shared by all WHO partners reporting SARS and SARS-like victims. A case definition was developed several months after the onset of the epidemic. The Centers for Disease Control (CDC) defined a suspect case of SARS as a person with onset of fever (temperature >38°C [100.4°F]) and lower respiratory tract symptoms within 10 days of either travel to an area with documented transmission of SARS or close contact with a person believed to have SARS. A probable cause was defined as a suspect case that also has chest radiographic findings of pneumonia, acute respiratory distress (ARDS), or an unexplained respiratory illness resulting in death, with autopsy findings of ARDS without identifiable cause. Suspect and probable cases were further classified based on laboratory findings as laboratory positive, laboratory negative or indeterminate, as shown in the following table 6:

Table 1. Centers for Disease Control and Prevention Case Definition for SARS[3,4]*

Clinical criteria
- Asymptomatic or mild respiratory illness
- Moderate respiratory illness
  - Temperature >100.4°F (>38°C) *and*
  - One or more clinical findings of respiratory illness (eg, cough, shortness of breath, difficulty with breathing, or hypoxia)
- Severe respiratory illness
  - Temperature >100.4°F (>38°C) *and*
  - One or more clinical findings of respiratory illness (eg, cough, shortness of breath, difficulty with breathing, or hypoxia)
  - AND
  - Radiographic evidence of pneumonia *or*
  - ARDS *or*
  - Autopsy findings consistent with pneumonia or ARDS without an identifiable cause

Epidemiological criteria
- Travel (including transit in an airport) within 10 days of onset of symptoms to an area with current or recently documented or suspected community transmission of SARS†
- OR
- Close contact within 10 days of onset of symptoms with a person known or suspected to have SARS infection

Laboratory criteria
- Confirmed
  - Detection of antibody to SARS-CoV in specimens obtained during acute illness or >21 days after illness onset *or*
  - Detection of SARS-CoV RNA by RT-PCR confirmed by a second PCR assay, by using a second aliquot of the specimen and a different set of PCR primers *or*
  - Isolation of SARS-CoV
- Negative
  - Absence of antibody to SARS-CoV in convalescent serum obtained >21 days after symptom onset
- Undetermined
  - Laboratory testing either not performed or incomplete

Case classification
- Probable case
  - Meets the clinical criteria for severe respiratory illness of unknown etiology with onset since November 1, 2002, and epidemiological criteria; laboratory criteria confirmed, negative, or undetermined
- Suspect case
  - Meets the clinical criteria for moderate respiratory illness of unknown etiology with onset since November 1, 2002, and epidemiological criteria; laboratory criteria confirmed, negative, or undetermined

*ARDS = acute respiratory distress syndrome; RT-PCR = reverse-transcriptase polymerase chain reaction; SARS = severe acute respiratory syndrome; SARS-CoV = SARS coronavirus.

†Travel criteria for suspect or probable US cases of SARS. Last date of illness onset for inclusion as a reported case: China (mainland), Hong Kong, Taiwan, Toronto, ongoing; Hanoi, Vietnam, May 25, 2003; Singapore, June 4, 2003.

The rapid collection and classification of data during and after the epidemic subsided has allowed the refinement of those indicators to include further description of clinical, physical, laboratory and radiographic findings7:

1. Clinical Signs and Symptoms: The median incubation period for SARS appeared to be four to six days, with most patients becoming ill within two to 10 days after exposure. The most common symptoms were fever, often accompanied by headache, myalgia, malaise, chills and rigor. The main component of SARS, respiratory symptoms, typically did not begin until after two to seven days after illness onset. The most common respiratory symptoms were lower respiratory tract symptoms, including cough and dyspnea. Gastrointestinal symptoms were reported in some cases.

2. Physical findings: the most frequent physical findings were tachypnea, tachycardia and hypoxemia. Although fever was commonly associated with SARS (to the extent that some public buildings rapidly acquired and installed automatic body tempera-

body temperature upon evaluation, even though other symptoms of SARS were already present.

3. Laboratory findings: hematologic abnormalities were among the most consistent laboratory findings reported in SARS patients; most patients had total leukocyte counts that were normal or slightly low, and 70-95 percent of patients had lymphopenia. Platelet counts were mildly depressed in 30-50 percent of all patients, and prolongation of the activated partial thromboplastin time was observed in 40-60 percent of patients; other common lab abnormalities included elevated lactate dehydrogenase in 70-90 percent of patients, elevated alanine aminotransferase levels in 20-30 percent, and elevated creatine phosphokinase in 30-40 percent of all patients.

4. Radiographic findings: Available data suggests that almost all reported SARS patients with laboratory evidence of SARS-CoV infection have radiographic evidence of pneumonia documented at some point during their illness. However, approximately 30 percent of chest X-rays may be normal at the time of first evaluation despite onset of symptoms. Aggregated data suggested the presence of radiographic evidence of SARS-CoV in 97 percent of all patients at day seven of onset of symptoms. CT appeared to be a more sensitive instrument than conventional X-rays; SARS patients who had normal X-rays early in their clinical course often had evidence of pneumonia by CT.

5. Clinical virology: The main laboratory tests available to diagnose SARS-COV infection utilized by public health authorities as a response to the epidemic were RNA detection through reverse transcriptase-polymerase chain reaction (RT-PCR) or real-time PCR and serologic testing for antibodies against SARS-CoV8. Despite the disputes regarding the reliability of PCR tests for SARS-CoV detection, the clinical means has been endorsed by other studies9. The CDC has endorsed the use of RT-PCR as a means of detection of SARS-CoV infection. This is working definition used by the CDC10:
   A. Laboratory confirmed SARS-CoV
      - Detection of any of the following by a validated test, with confirmation in a reference laboratory:
      - Serum antibodies to SARS-CoV in a single serum specimen, or
      - A four-fold increase in SARS-CoV antibody titer between acute and convalescent-phase serum specimens tested in parallel or
      - Isolation in cell culture of SARS-CoV from a clinical specimen, with confirmation using a test validated by CDC or;
      - Detection of SARS-CoV RNA by RT-PCR validated by CDC, with confirmation in a reference laboratory, from:
         - Two clinical specimens from different sources, or
         - Two clinical specimens collected from the same source on two different days

The CDC has developed and validated an enzyme immunoassay (EIA) for detection of serum antibody to SARS-CoV and an RT-PCR assay for detection of SARS-CoV. The CDC, however, considers detection of the SARS-CoV antibody the most reliable indicator of the infection11.

EPIDEMIOLOGY:

Tacking the causative agent of disease and route(s) of transmission:

Despite the development of this array of indicators, detection of the SARS-CoV infection mainly remains in the realm of epidemiological investigation. As with other causes of bacterial and viral pneumonia, clinical findings in patients with SARS cannot accurately predict the causative agent. Additional refinements in the detection of the causative agent are required to determine whether the constellation of clinical findings alone can be used to discriminate accurately between SARS and other respiratory diseases. Many of the clinical and laboratory features of SARS are similar to other forms of viral pneumonia. This makes tracking suspect SARS cases and determining routes of infection a complicated task12.

Once again the rapid public health response allowed the collection and dissemination of crucial information allowing the identification of probable cases and routes of transmission. The following information has been validated through repeated epidemiological observation over the course of the epidemic and its aftermath13:

1. Direct contact: the fact that the majority of new infections occurred in close contact of patients, such as household members, healthcare workers or other patients not protected, indicates that the virus is predominantly spread by droplets or by direct and indirect contact. Airborne spread of SARS, however, does not seem to be a major route of transmission, despite conflicting evidence linked to the apparent airborne transmission in the Hong Kong/Hotel Metropole infection cluster. There are currently no indications that any goods, products or animals arriving from areas with SARS outbreaks pose a risk to public health, leading the WHO to not recommend any restriction in animal movement from epidemic zones.

2. Asymptomatic patients: There are few data as to asymptomatic individuals can transmit the infection. Preliminary findings suggest that developers of mild symptoms may have the SARS-CoV antibodies without developing SARS. There is at present no direct evidence of contagion from an asymptomatic patient.

3. Symptomatic patients: The weight of evidence suggests that only symptomatic patients may spread the SARS virus efficiently. However, early evidence from Singapore suggests that the rate of transmission, though considerable, is not explosive: 81 percent of all probable SARS cases in Singapore had no evidence of transmission of a clinically identifiable illness to other persons. In comparison with other infectious diseases that are spread via the respiratory route, SARS seems to be moderately transmissible.

4. Superspreaders: The term "superspreading" has been used to describe situation in which a single individual has directly infected a large number of other individuals. In the Singapore epidemic, of the first 201 probable cases reported, 103 were infected by just five source cases. The most probable explanation for the phenomenon of superspreading is extensive viral shedding by the patients. This may be due to advanced disease or possibly co-morbidities that result in high viral loads. However, there is need of additional data to come to definite conclusions in order to understand why, under certain circumstances, the spread of SARS is extremely efficient.

5. High-risk activities: The rapid spread of SARS among healthcare workers in Hanoi, Vietnam and in Hospital in Hong Kong confirmed the potentially highly contagious nature of the virus. Medical personnel, physicians, nurse and hospital workers are among those commonly infected. Attack rates as high as 50 percent have been reported. In particular, diagnostic and therapeutic procedures inside the hospitals, such as diagnostic sputum induction, bronchoscopy, endotracheal intubation, and airway suction are potent aerosol generating procedures, and are now recognized as high-risk activities. The high-risk nature of activities generating potent aerosol potential is validated by the recently publicized outbreak of SARS affecting lab workers in China14.

6. Transmission during quarantine: There has been at least one report of SARS-CoV transmission during quarantine. This indicated the risk of grouping suspected SARS cases with real SARS cases in that the uninfected individual may become infected during the isolation and quarantine period.

7. Final observations: The SARS virus is not easily transmissible outside of certain settings. For a major local outbreak to occur there needs to be:
   A. An infectious patient, and
   B. A close community or "tribe," i.e., healthcare workers, military populations, travel groups, religious gatherings or funerals, with close interactions.

The foregoing suggests the crucial importance of appropriate tracking and linkage of suspected and probable SARS patients, and strict preventive and remedial measures. These will be discussed in a subsequent section of this paper.

ATTACK RATES:

Even though several estimations of SARS-CoV attack rates have been made by public health authorities worldwide, a study published in the NEJM using cases and controls traveling in airplanes with known SARS-infected individuals is very compelling due to the built-in control for confounding factors. The researchers chose three different instances where airline passengers were found to sit at varying distances to SARS-infected patients. The researchers controlled for the infectious nature of the index passenger, previous pulmonary infections in cases and controls on board and distance from the seating place of the index patient. After one flight carrying a symptomatic person and 119 other persons, laboratory-confirmed SARS developed in 16 persons, two others were given diagnoses of probable SARS, and four were reported to have SARS but could not be interviewed. Among the 22 persons with illness, the mean time from the flight to the onset of symptoms was four days (range, two to eight), and there were no recognized exposures to patients with SARS before or after the flight. Illness in passengers was related to the physical proximity to the index patient, with illness reported in eight of the 23 persons who were seated in the three rows in front of the index patient, as compared with 10 of the 88 persons who were seated elsewhere (relative risk, 3.1; 95 percent confidence interval, 1.4 to 6.9). In contrast, another flight carrying four symptomatic persons resulted in transmission to at most one other person, and no illness was documented in passengers on the flight that carried a person who had pre-symptomatic SARS. This, in turn, lead to the conclusion that transmission of SARS may occur on an aircraft when infected persons fly during the symptomatic phase of illness.15.

METHOD(S) OF CONTROL/PREVENTION:

The CDC has issued the following core recommendations as key elements for control and prevention of SARS-CoV epidemic recurrence:

1. Command and control
   a. Goals:
      i. Determine and establish operational authority for a response
      ii. Establish an incident management structure for the response to a SARS outbreak, supported by adequate information systems
      iii. Determine and establish legal authority for a response to a SARS outbreak
2. Surveillance
   a. Goals:
      i. Maximize early detection of cases and clusters of respiratory infections that might signal the global re-emergence of SARS-CoV disease while minimizing unnecessary laboratory testing, implementation of control measures and social disruption
      ii. If SARS-CoV transmission recurs, maintain prompt and complete identification and reporting of potential cases to facilitate outbreak control and management
      iii. Identify and monitor contacts of cases of SARS-CoV disease to enable early detection of illness in persons at greatest risk
3. Preparedness
   a. Goals:
      i. Rapidly identify and isolate all potential SARS patients
      ii. Implement infection control practices and contact tracing to interrupt SARS-CoV transmission
      iii. Ensure rapid communication within healthcare facilities and between healthcare facilities and health departments
4. Community containment measures, including non-hospital isolation and quarantine
   a. Goal:
      i. Prevent transmission of SARS-CoV through use of a range of community containment strategies chosen to provide maximum efficacy based on the characteristics of the outbreak while minimizing the adverse impacts on civil liberties
5. Prevention of international travel-related transmission risk
   a. Goals:
      i. Prevent the introduction of SARS-CoV (and spread from an introduction) into the United States from SARS-affected areas
      ii. Prevent exportation of SARS-CoV from the United States if domestic transmission presents and increased risk of exportation
      iii. Reduce the risk of SARS-CoV disease among outbound travelers to SARS-affected areas
      iv. Prevent the transmission of SARS-CoV to passengers on a conveyance with a SARS patient, and evaluate and monitor other passengers to detect SARS-like illness and prevent further spread

6. Laboratory Diagnostics
    a. Goals:
        i. Provide the public health community with ready access to high-quality SARS-CoV diagnostics
        ii. Ensure that SARS-CoV laboratory diagnostics are used safely and appropriately and that results are interpreted correctly
7. Communication and Education
    a. Goals:
        i. Instill and maintain public confidence in the nation's public health system
        ii. Contribute to the maintenance of order, minimization of public panic and fear and facilitation of public protection
        iii. Provide accurate, timely and comprehensive information about the SARS-CoV epidemic and disease
        iv. Address rumors, inaccuracies, and misperceptions as quickly as possible, and prevent stigmatization of specific groups
8. Infection control in healthcare, home and community settings
    a. Goals:
        i. Ensure early recognition of patients at risk for SARS-CoV disease
        ii. Prevent transmission of SARS-CoV by implementing appropriate infection control precautions
9. Information technology
    a. Goal:
        i. Deploy an integrated data management system that efficiently and effectively supports SARS outbreak response needs at the federal, state and local levels.

These basic measures have been widely disseminated by the CDC and WHO as an elementary template for the prompt detection and containment of SARS-CoV.

PUBLIC HEALTH LAW OBSERVATIONS:

An epidemic involving SARS-CoV in the United States will test the limits of the public health legal infrastructure. The eventuation of an epidemic of major proportions would force public health authorities to utilize all legal means at their disposal to control and contain the epidemic.

This possibility raises serious questions that must be properly answered in order to prevent unnecessary loss of life, economic activity and social interaction. Two solutions have been proposed: one is encompassed by the MSEHPA[17], the other by the defenders of a more traditional approach to the application of state police power as the proper means to deal with such an emergency[18]. The discussion revolving around these two differing proposals is far from theoretical. The MSEHPA proposes a balanced approach to infection control including comprehensive legal protection to individuals, including court hearings to contest isolation and quarantine orders. This may result inadequate to properly control, track and detain potential spreaders. The traditional police power approach, on the other hand, offers a much more flexible response capability, which may be hampered by antiquated laws and judicial interference with administrative activities.

A prompt response to this legal debate is needed. Public health law will be an indispensable component of a truly effective public health response to SARS.

CONCLUSION:

A recent controlled outbreak of SARS highlights the critical importance of maintaining a vigilant attitude towards this disease. Massive media have, unfortunately, done a poor job in properly illustrating the proper scope of the disease and the risks associated with it.

Concerned governments must develop prophylactic plans to educate and sensitize the population at large about the contagious routes, symptoms and risks of SARS. The almost automatic reappearance of facemasks in China upon preliminary suggestions of a renewed epidemic is a hallmark of an aware population. Such measures must be strengthened and amplified until such time as more reliable markers of the disease are developed and/or an effective vaccine is produced for those populations at risk for the disease.

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